The goal in growing crystals for a single crystal X-ray diffraction experiment is to grow single crystals (obviously) of suitable size: 0.2 - 0.4 mm in at least two of the three dimensions.

General Considerations (factors that affect crystallization):

Solvent.

Choose a solvent in which your compound is moderately soluble. If the solute is too soluble, this will result in small crystal size. Avoid solvents in which your compound forms supersaturated solutions. supersatuated solutions tend to give crystals which are too small in size.

Nucleation.

The fewer sites at which crystals begin to grow will result in fewer crystals each of larger size. This is desirable. Conversely, many nucleation sites results in a smaller average crystal size, and is not desirable. In many recrystallizations ambient dust in the laboratory provide sites of nucleation. It is important to minimize dust or other extraneous particulate matter in the crystal growing vessel.

Mechanics/Time.

Mechanical disturbance of the crystal growing vessel results in smaller crystals. Let the crystals grow with a minimum of disturbance. This means: Don't try to grow crystals next to your vacuum pump, and don't pick up the vessel everyday to check on how your crystals are growing. Set up the crystal growing attempt, in a quiet, out of the way place and forget about it (if possible!) for a week. Crystals fully recognize that patience is a virtue and will reward those who practice it.

Techniques

Slow Evaporation. Simplest way to grow crystals and works best for compounds that are not sensitive to ambient conditions in the laboratory. Prepare a solution of the compound in a suitable solvent. The solution should be saturated or nearly saturated. Transfer the solution to a CLEAN crystal growing dish and cover. The covering for the container should not be air tight. Aluminium foil with some holes poked in it works well, or a flat piece of glass with microscope slides used as a spacer also will do the trick. Place the container in a quiet out of the way place and let it evaporate. This method works best where there is enough material to saturate at least a few milliliters of solvent.

Slow Cooling. This is good for solute-solvent systems which are less than moderately soluble and the solvent's boiling point is less than 100 ˚C. Prepare a saturated solution of the compound where is the solvent is heated to just it's boiling point or a just below it. Transfer the solution to a CLEAN large test tube and stopper. Transfer the test tube to a Dewar flask in which hot water (heated to a temperature of a couple of degrees below the solvent boiling point). The water level should exceed the solvent level in the test tube, but should not exceed the height of the test tube. Stopper the Dewar flask with a cork stopper and let the vessel sit for a week. A more elaborate version of this involves a thermostated oven rather than a Dewar flask.

Variations on Slow Evaporation and Slow Cooling. If the above two techniques don’t yield suitable crystals from single solvent systems, one may expand these techniques to binary or tertiary solvent systems. The basic rationale for this is by varying the solvent

composition one may inhibit growth of certain crystal faces and promote the growth of other faces, yielding crystals of suitable morphology and size. If you choose this route for growing crystals, it absolutely necessary to record the solvent composition you use! If crystal growing is an art, growing crystals from binary or tertiary solvent mixtures is that much more imprecise. Remember reproducibility is paramount in science.

Vapor Diffusion. This method is good for milligram amounts of material. A solution of the substance is prepared using solvent S1 and placed in test tube T. A second solvent, S2, is placed in a closed beaker, B. S2 is chosen such that when mixed with S1 the solute will become less soluble. The test tube containing S1 is then placed in the beaker and the beaker is sealed. Slow diffusion of S2 into T and S1 out of T will cause crystals to form. If S2 is more volatile than S1 the solvent level will increase and prevent microcrystalline crusts from forming on the sides of T.

Solvent Diffusion (Layering Technique). This method also is good for milligram amounts of materials which are sensitive to ambient laboratory conditions (air, moisture). Dissolve the solute in S1 and place in a test tube. **Slowly** dribble S2 into the tube so that S1 and S2 form discreet layers. This will only be successful if 1) The density of S2 < S1 and 2) Care is exercised in creating the solvent layer. I have found that a syringe is the best way to add the second solvent. The narrower the tube , the easier it is to build up the layer. Five millimeter NMR tubes are excellent vessels to use for this crystal growing technique. CH2Cl2/Et2O is a good solvent combination to try this method (if your compound is insoluble in ether).

Reactant diffusion. This similar to the other diffusion methods except that solutions of the reactants are allowed to diffuse into one another. If the product of the reaction is insoluble, crystals of the product will form where the reactants mix. There is mention in the literature of this technique being used with diffusion in silica gels (see *Acta. Cryst.* **19**, 483, **(1965)**).

Sublimation. Simply seal a sample under vacuum into a glass tube and placing the tube into an oven for a few days or weeks. Larger crystals tend to grow at the expense of smaller ones. If it doesn't work raise the temperature of the oven or move to another hotter one. In some cases a tube furnace can be used. The tube can be placed close to one end of the furnace so that there is a mild temperature gradient.

Convection. One may attempt to grow crystals by convection by creating a thermal gradient in the crystal growing vessel. The idea behind this method is that the solution becomes more saturated in the warm part of the vessel and is transferred to the cooler region where nucleation and crystal growth occur. To create the convection one may use either local heating or local cooling. The velocity of the convection current is proportional to the thermal gradient across the vessel. Care must be taken to not make the gradient too large, or the convection will be too rapid and inhibit crystal growth.
To use local cooling, simply take a flat bottomed crystal growing dish (similar to what one would use for slow evaporation) and place one side of it against the heat sink. Normally, simply placing the vessel against a cold outside window will suffice. Notice

that the heat sink needs to be against the side of the vessel. Laying the vessel on a cool surface will not induce convection. There are also devices you can make for this purpose: An inexpensive thermal gradient device can be constructed which can be used to obtain good crystals of "difficult to crystallize" compounds. To make the device do the following: Cut off the tip of a Pasteur pipet about one cm above the beginning of the narrowing part, and then heat seal the small end, you get a nice cheap thermal gradient vial. Place a slurry of your material in a relatively poor solvent in the vial and centrifuge to pack the undissolved material in the tip. After centrifuging, you have a pellet of solid (~5mm) in the tip, covered by clean "poor" solvent. Seal the vial with teflon tape and parafilm. I make the heater from the small cylinder shaped ceramic resistors which are usually available from the electronics shop. I found some green ones of 100 ohms which are a good size. Place just the tip of the vial with the solid pellet in the heater, with the vial at ~45 degrees from vertical. Apply voltage to get maybe 50 C at the resistor, and you have a nice thermal gradient up the vial. With luck, you get crystals growing up the vial. It seems important to make sure all the amorphous material is packed down...no powder where you want the crystals to grow.

Co-crystallants. If you are not getting suitable crystals from other crystallization methods, you can try to cocrystallize your compound with a "crystallization aid". In the literature (see *J. Amer. Chem. Soc.* **1988**, *110*, 639- 640) triphenylphosphine oxide (TPPO) has been used as a cocrystallant for organic molecules which are proton donors. Obviously, this method of crystallization is not for all compounds, but for those it is, the results may be rewarding. Essentially this method of crystal growing is the same as slow evaporation except that an equimolar amount of TPPO is added to the solution. I suppose that the other crystallization methods outlined above would also work with this method.

Counterions. If your compound is ionic, and is not giving suitable crystals with a given counterion, perform a metathesis reaction to change the counterion. Very often the crystal quality will improve when a different counterion used. Ions of similar size tend to pack together better and subsequently give better crystals. In addition, you might also get more desirable physical properties for your crystal. For example, the sodium salt of your compound might be hygroscopic, but the tetramethyl ammonium salt might not be or at least, less so. When selecting possible counterions, avoid ions which contain large non-rigid groups (like tetrabutyl ammonium).

Ionization of Neutral Compounds. If your compound is neutral and contains proton donor or acceptor groups, better crystals may grown by first protonating or deprotonating (as applicable) your compound. The ionic form of your compound could then take advantage of hydrogen bonding to yield better crystals

If you are sure your compound is pure and a crystal growing technique is not giving suitable crystals change the solvent or the method. If one system does not yield suitable crystal after a couple of tries it is not going to yield good crystals after the tenth or hundredth time. Be intuitive, imaginative, but above all else stick to the basics - no dust, disturbance and a lot of patience.

Source: http://xray.chem.ualberta.ca/xray/GrowXtal.html